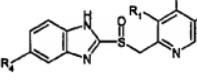
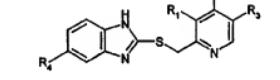




(51) International Patent Classification 6 : C07D 401/12		A1	(11) International Publication Number: WO 99/47514			
(21) International Application Number:	PCT/EP99/01574		(12) International Publication Date: 23 September 1999 (23.09.99)			
(22) International Filing Date:	11 March 1999 (11.03.99)					
(30) Priority Data:	9805558.5 17 March 1998 (17.03.98)	GB				
(71) Applicant (for all designated States except US):	KNOLL AKTIENGESELLSCHAFT (DE/DE); D-67061 Ludwigshafen (DE).					
(72) Inventors; and						
(75) Inventors/Applicants (for US only):	BRENNAN, James, Patrick [GB/GB]; R4 Pennyfoot Street, Nottingham NG1 1GF (GB). TURNER, Andrew, Timothy [GB/GB]; R4 Pennyfoot Street, Nottingham NG1 GFI (GB).					
(74) Agents:	MILLER, Thomas, Kerr et al.; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).					
(54) Title:	CHEMICAL PROCESS FOR THE PRODUCTION OF SULPHINYL DERIVATIVES BY OXIDATION OF THE CORRESPONDING CO-DERIVATIVES WITH PERBORATES					
(57) Abstract	<p>A process for the preparation of a compound of formula (I) in which R₁, R₂, R₃ and R₄ represent: a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or c) (R₁=OCH₃; R₂=OCH₂CF₃; R₃=H and R₄=OCH₂F₂) respectively and pharmaceutically acceptable salts thereof, comprising reacting a compound of formula (II) in which R₁, R₂, R₃ and R₄ represent a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or c) R₁=OCH₃; R₂=OCH₃; R₃=H and R₄=OCH₂F₂ respectively, with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0 °C to the boiling point of the liquid diluent employed.</p>					
(81) Designated States:	AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).					
(43) International Publication Date:	23 September 1999 (23.09.99)					
Published						
With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.						
(I)						
(II)						

FOR THE PURPOSES OF INFORMATION ONLY

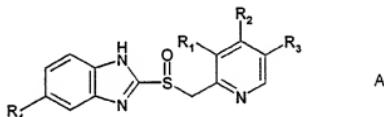
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Greece	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Malta	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	KR	Kazakhstan	RU	Russian Federation		
CZ	Czech Republic	LC	Saint Lucia	SD	Sudan		
DE	Germany	LI	Liechtenstein	SE	Sweden		
DK	Denmark	LK	Sri Lanka	SG	Singapore		
EE	Estonia	LR	Liberia				

CHEMICAL PROCESS FOR THE PRODUCTION OF SULPHINYL DERIVATIVES BY OXIDATION OF THE CORRESPONDING THIO-DERIVATIVES WITH PERBORATES

The present invention describes an improved process for the preparation of substituted 2-(2-pyridylmethyl)sulphanyl-1*H*-benzimidazoles particularly omeprazole, 5 lansoprazole and pantoprazole by oxidising the corresponding substituted 2-(2-pyridylmethylthio)-1*H*-benzimidazole.

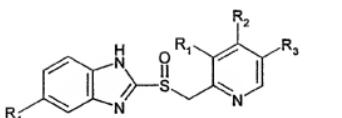
Several proton-pump inhibitors, which are useful in the treatment of duodenal ulcers, of formula A are known. These include omeprazole ($R_1=CH_3$; $R_2=OCH_3$; 10 $R_3=CH_3$; $R_4=OCH_3$) which is described in EP5129, lansoprazole ($R_1=CH_3$; $R_2=OCH_2CF_3$; $R_3=H$; $R_4=H$) which is described in EP174,726 and pantoprazole ($R_1=OCH_3$; $R_2=OCH_3$; $R_3=H$ and $R_4=OCHF_2$) which is described in EP166,287.



Many methods for preparing such compounds by the oxidation of the 15 corresponding 2-(2-pyridylmethylthio)-1*H*-benzimidazole have been described. Examples of the oxidising agents used are 3-chloroperoxybenzoic acid (WO91/18895, EP533752, US5,386,032, ES43816 and EP484265), magnesium monoperoxyphthalate (EP533264 and US5,391,752), ammonium molybdate (EP484,265), iodosobenzene (ES539793), methyliodosobenzene (ES540147), 20 sodium periodate (ES550070) and vanadium oxide (EP302720).

However, there remains a need for a cheap and efficient process for oxidising 2-(2-pyridylmethylthio)-1*H*-benzimidazoles which is reliable, produces waste streams which are easily disposed of without causing harm to the environment and produces 25 a stable final product.

The present invention provides a process for the preparation of a compound of formula I

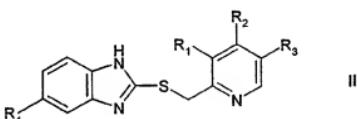


in which R₁, R₂, R₃ and R₄ represent

5 a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or
 b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or
 c) (R₁=OCH₃; R₂=OCH₃; R₃=H and R₄=OCHF₂) respectively
 and pharmaceutically acceptable salts thereof

comprising reacting a compound of formula II

10



in which R₁, R₂, R₃ and R₄ represent

15 a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or
 b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or
 c) (R₁=OCH₃; R₂=OCH₃; R₃=H and R₄=OCHF₂) respectively

with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed.

20

Suitably the perborate salt is a metallic perborate salt or an ammonium perborate salt. The perborate salt may be anhydrous or hydrated. Preferably the perborate salt is potassium or sodium perborate. More preferably the perborate salt is sodium perborate. Most preferably the perborate salt is sodium perborate monohydrate or sodium perborate tetrahydrate.

25

Suitably the amount of perborate salt employed in the process is in the range of 0.8 to 3 moles per mole of the compound of formula II employed in the process.

Preferably the amount of perborate employed is in the range 0.95-2.0 moles per mole of the compound of formula II employed in the process. More preferably the amount of perborate employed is in the range 1.0-1.9 moles per mole of the compound of formula II employed in the process for example 1.1-1.5 moles per mole of the compound of formula II. Most preferably the amount of perborate employed is in the range 1.4-1.8 moles per mole of the compound of formula II employed in the process.

The purpose of the liquid diluent is to allow contact between the compound of formula II and the perborate salt at the required temperature. Any liquid diluent, which is inert to the reactants, in which this purpose is achieved may be used.

Preferably the liquid diluent is selected from water, a C₁₋₄ alcohol, toluene, tetrahydrofuran, acetone, a C₂₋₆ diol, a C₃₋₆ triol, ethyl acetate or mixtures thereof. More preferably the liquid diluent is a water/alcohol mixture, for example a water/methanol or a water/ethanol mixture. Most preferably the diluent is a water/methanol mixture optionally containing toluene.

Preferably the process is carried out at a pH in the range of 8.5 to 12. More preferably 10 to 12. Most preferably the process is carried out at a pH in the range of 10 to 11.

Suitably the pH of the process is controlled by the addition of a base for example an alkali metal hydroxide an alkali metal carbonate, an alkali metal bicarbonate or an amine e.g. ammonia or an organic amine or mixtures thereof. Preferably the base is sodium hydroxide.

It will be appreciated by those skilled in the art that when the reaction is carried out at high pH a salt of the desired product may be obtained. Lowering the pH of the reaction mixture, for example by addition of an acid or preferably of a less basic base, allows the isolation of the compound of formula I as the free heterocycle.

Preferably the process is carried out at a temperature in the range of 0 to 150°C and more preferably in the range of 15 to 115°C. Most preferably the process

is carried out at a temperature in the range of 40 to 55°C, particularly at a temperature in the range of 45 to 50°C.

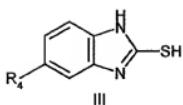
The process of the present invention has several advantages over previously described oxidation processes. The reagents employed are cheap, non-hazardous and environmentally friendly, for example sodium perborate is used in domestic washing powder, in mouth washes and in cleaning fluids for contact lenses. Sodium perborate has exceptional storage stability and is not shock sensitive. The process gives good yields reproducibly and provides a product of high purity which is chemically more stable than the products of other oxidation processes especially those carried out in acidic conditions. In addition environmentally friendly liquid diluents may be used.

The process of the present invention has two further advantages over the prior art processes. Firstly, this process step may be combined with the previous process step and thus avoid isolation of the compound of formula II. This leads to cost reduction in the process through improved processing times. Secondly, in comparative experiments sodium perborate appears to give fewer impurities arising from over-oxidation, for example formation of a sulphone, or an *N*-oxide, or a sulphone *N*-oxide, than previously known oxidants, for example 3-chloroperoxybenzoic acid.

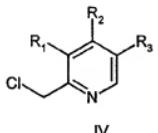
The desired product can be isolated from the reaction mixture and purified by conventional means e.g. extraction and recrystallisation or filtration followed optionally by recrystallisation.

In a preferred process of the present invention a compound of formula IIa is reacted with sodium perborate in a mixture of water and methanol at a pH in the range of 8.5 to 10 at a temperature in the range of 15 -115°C to give a compound of formula Ia (omeprazole).

In a more preferred process of the present invention the compound of formula II is prepared by reacting a compound of formula III



or a salt thereof in which R₄ is as previously defined with a compound of formula IV



5 or a salt thereof in which R₁, R₂, and R₃ are as previously defined, in a second liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the second liquid diluent employed and is then reacted with a perborate salt without isolation.

10 The purpose of the second liquid diluent is to allow contact between the compound of formula III and the compound of formula IV at the required temperature. Any liquid diluent, which is inert to the reactants, in which this purpose is achieved may be used. Preferably the reaction of III and IV is carried out at a temperature in the range of 10-100°C, preferably at a temperature in the range of 20-80°C and more 15 preferably at a temperature in the range of 40-60°C.

20 Preferably the second liquid diluent is selected from water, a C₁₋₄ alcohol, toluene, tetrahydrofuran, acetone, a C₂₋₆ diol, a C₃₋₆ triol, ethyl acetate or mixtures thereof. More preferably the second liquid diluent is a water/alcohol mixture, for example a water/methanol or a water/ethanol mixture. Most preferably the diluent is a water/methanol mixture optionally containing toluene. Especially preferably the second liquid diluent is the same as the first liquid diluent. This avoids further processing for example diluent exchange.

In a preferred embodiment the compound of formula III is present as the free thiol, initially, and the process is carried out in the presence of a base. Preferably the base is an alkali metal hydroxide for example sodium hydroxide or potassium hydroxide. More preferably the base is sodium hydroxide.

5

In a preferred embodiment the compound of formula IV is present as a salt and sufficient base is used in the process to neutralise the salt of the compound of formula IV and to form a salt of the compound of formula III. Preferably the salt of the compound of formula IV is the hydrochloride salt, the hydrobromide salt, the acetate salt, the nitrate salt or a salt of sulphuric acid or the salt of a phosphoric acid. Most 10 preferably the salt is the hydrochloride salt.

Preferably the amount of base employed is in the range of 2.0 to 5.0 moles per mole of the compound of formula III. More preferably the amount of base 15 employed is in the range of 3 to 4 moles per mole of the compound of formula III.

In a preferred embodiment of the process a purification solvent is added at the end of the oxidation reaction. The purification solvent has been found to remove certain impurities from the crude reaction product by dissolving these impurities so 20 that on filtration the product obtained requires fewer recrystallisations than would otherwise be necessary. This provides time and energy and therefore cost savings in the process. The purification solvent also aids the filtration process by changing the physical nature of the product so that it can be more readily filtered. Preferably the purification solvent is immiscible with the liquid diluent.

25

Preferred purification solvents are hydrocarbons, including aliphatic and aromatic hydrocarbons, and ethers, particularly di(C₁₋₆alkyl) ethers in which the alkyl groups are the same or different, and esters, for example ethyl acetate and mixtures thereof. More preferably the purification solvent is *tert*-butyl methyl ether, diisopropyl 30 ether, hexane, heptane or toluene and mixtures thereof. Most preferably the purification solvent is *tert*-butyl methyl ether, diisopropyl ether or hexane and mixtures thereof. Especially preferably the purification solvent is *tert*-butyl methyl ether or diisopropyl ether.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each of these Examples was characterised by one or more of the following procedures: high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy, infrared spectroscopy 5 and high resolution mass spectroscopy. The compounds of formula II, III and IV used in the Examples were either commercially available or were prepared by the methods given in EP5129, EP174,726 or EP166,287 which are incorporated herein by reference.

10 Example 1

A solution of sodium hydroxide pellets (0.32 g), sodium perborate tetrahydrate (1.43 g) and water (35 ml) was prepared by stirring and heating the mixed components until a solution was obtained, and was then added dropwise with 15 stirring over 2.5 hours to a solution of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]thio)-1*H*-benzimidazole (2.0 g) in methanol (20 ml) and toluene (2 ml) which was boiling under reflux. The methanol was removed under reduced pressure and the residue was cooled to 50°C and then added to saturated sodium bicarbonate solution (20 ml). The mixture was extracted with dichloromethane 20 (2 x 10 ml), the combined extracts were dried, filtered and evaporated to give 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphiny)-1*H*-benzimidazole (1.60 g). Yield 86.5%.

25 Example 2

A solution was prepared by dissolving sodium hydroxide pellets (17.7 g) and sodium perborate tetrahydrate (68.3 g) in water (1085 ml) with stirring and heating and this solution was then added dropwise to a solution of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]thio)-1*H*-benzimidazole (83.4 g) in 30 methanol (834 ml) whilst the mixture was boiled under reflux. The methanol was removed under reduced pressure and the residue was cooled to 50°C and then added to saturated sodium bicarbonate solution (830 ml). The mixture was cooled to 30°C and extracted with dichloromethane (2 x 400 ml). The combined dichloromethane extracts were dried over magnesium sulphate, filtered and

evaporated to give 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl]-1*H*-benzimidazole (74.0 g, 84.6% yield). This material was stirred in ethyl acetate (222 ml) for 1 hour then filtered. The residue was washed with ethyl acetate (2 x 25 ml) and dried to give a product which was 96.7% pure by HPLC.

5

Example 3

10 A solution of sodium hydroxide (1.0 g) and sodium perborate tetrahydrate (3.8 g) in water (65.0 ml) was prepared by heating and stirring. This solution was then added dropwise to a solution of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-ylmethylthio]-1*H*-benzimidazole (5.0 g) in methanol (50.0 ml) which was being boiled over 2 hours at reflux with stirring. The mixture was stirred and boiled for a further 15 minutes, then the methanol and water were removed under reduced pressure to give a residue which was cooled to 50°C and added to saturated sodium bicarbonate solution (50.0 ml). This mixture was cooled to 30°C and then extracted with dichloromethane (2 x 25 ml). The combined extracts were dried, filtered and evaporated to give 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinylmethylsulphinyl]-1*H*-benzimidazole (4.8 g, 92.3% yield). The purity of this material was 90.3% by HPLC. This solid was stirred with ethyl acetate (14.4 ml) for 1 hour and then the solid collected by filtration, washed with ethyl acetate and dried to give material which was 91.4% pure by HPLC.

Example 4

25 A solution of sodium hydroxide (9.8 g) and sodium perborate tetrahydrate (37.3 g) in water (638.3 g) was prepared by heating and stirring. This solution was then added dropwise over 2.5 hours to a solution of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-ylmethylthio]-1*H*-benzimidazole (49.1 g) in methanol (491.0 ml) which was being boiled at reflux with stirring. The mixture was stirred and boiled for a further 15 minutes, then the methanol and water were removed under reduced pressure to give a residue which was cooled to 50°C and added to saturated sodium bicarbonate solution (491 ml). This mixture was cooled to 30°C and then extracted with dichloromethane (2 x 245.5 ml). The combined extracts

were dried, filtered and evaporated to give 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinylmethylsulphiny]-1*H*-benzimidazole in quantitative yield.

Example 5

5

In a similar manner to Example 1, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methylthio]-1*H*-benzimidazole is reacted with sodium perborate to give 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphiny]-1*H*-benzimidazole.

10 Example 6

A mixture of 5-methoxy-2-mercaptop-1*H*-benzimidazole (198.8 g), methanol (380 ml) and water (760 ml) was stirred while sodium hydroxide solution (215 ml, 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a 15 solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (245 g) in water (1136 ml) was added over 1 hour. The mixture was stirred at 45-50°C for 2 hours and then sodium perborate tetrahydrate (202.4 g) was added. The mixture was stirred at 45-50°C for 18 hours. Further sodium perborate tetrahydrate (16 g) was added and the mixture was stirred for a further 4 hours. The mixture was cooled 20 to 30-35°C and sodium hydrogen carbonate (221.9 g) was added followed by water (763.4 ml) and *tert*-butyl methyl ether (763.4 ml). The mixture was stirred vigorously for 2 hours then filtered to give a product which was washed with *tert*-butyl methyl ether (500 ml) and then dried under vacuum at 45-50°C for 21 hours to give 25 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methylsulphiny]-1*H*-benzimidazole (293.4 g, 77% yield, purity by HPLC 98.3%).

Example 7

A mixture of 5-methoxy-2-mercaptop-1*H*-benzimidazole (4.3 g), methanol 30 (8.4 ml) and water (16.7 ml) was stirred while sodium hydroxide solution (4.7 ml, 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (5.3 g) in water (25 ml) was added over 35 minutes at 45-50°C. The mixture was stirred at 45-50°C for 1.75 hours and then sodium perborate tetrahydrate (4.5 g) was added.

The mixture was stirred at 45-50°C for 20 hours. Further sodium perborate tetrahydrate (0.35 g) was added and the mixture was stirred at 45-50°C for a further 3 hours. A final batch of sodium perborate tetrahydrate (0.35 g) was added and the mixture stirred for a further 2 hours at 45-50°C. The mixture was cooled to 35°C and 5 sodium hydrogen carbonate (4.9 g) was added followed by water (16.7 ml) and diisopropyl ether (16.2 ml). The mixture was stirred rapidly at 20-25°C for 1.5 hours. The mixture was filtered to give a product which was washed with water and dried under vacuum at 45-50°C to give 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphiny]-1*H*-benzimidazole (6.5 g, 78.9% yield, purity by HPLC 95.5%).

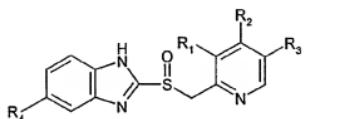
10

Example 8

A mixture of 5-methoxy-2-mercaptop-1*H*-benzimidazole (4.3 g), methanol (8.4 ml) and water (16.7 ml) was stirred while sodium hydroxide solution (4.7 ml, 15 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (5.3 g) in water (25 ml) was added over 35 minutes at 45-50°C. The mixture was stirred at 45-50°C for 1.75 hours and then sodium perborate tetrahydrate (4.5 g) was added. The mixture was stirred at 45-50°C for 20 hours. Further sodium perborate 20 tetrahydrate (0.35 g) was added and the mixture was stirred at 45-50°C for a further 3 hours. The mixture was cooled to 35°C and sodium hydrogen carbonate (4.9 g) was added followed by water (16.7 ml) and hexane (16.7 ml). The mixture was stirred rapidly at 20-25°C for 1.5 hours. The mixture was filtered to give a product which was washed with water and dried under vacuum at 45-50°C to give 25 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphiny]-1*H*-benzimidazole (6.6 g, 80.4% yield, purity by HPLC 94.45%).

CLAIMS

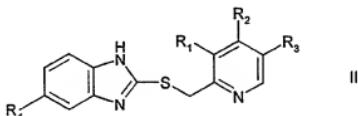
1. A process for the preparation a compound of formula I



in which R₁, R₂, R₃ and R₄ represent

- a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or
- b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or
- 10 c) (R₁=OCH₃; R₂=OCH₃; R₃=H and R₄=OCHF₂) respectively and pharmaceutically acceptable salts thereof

comprising reacting a compound of formula II



in which R₁, R₂, R₃ and R₄ represent

- a) (R₁=CH₃; R₂=OCH₃; R₃=CH₃; R₄=OCH₃) or
- b) (R₁=CH₃; R₂=OCH₂CF₃; R₃=H; R₄=H) or
- c) (R₁=OCH₃; R₂=OCH₃; R₃=H and R₄=OCHF₂) respectively

20

with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed.

25 2. A process as claimed in claim 1 wherein the perborate salt is sodium

perborate.

3. A process as claimed in either claim 1 or claim 2 in which the amount of perborate salt employed in the process is in the range of 0.8 to 3 moles per mole of the compound of formula II employed in the process.

5 4. A process according to any previous claim in which the liquid diluent is selected from water, a C₁₋₄ alcohol, toluene, tetrahydrofuran, acetone, a C₂₋₆ diol, a C₃₋₆ triol, ethyl acetate or mixtures thereof.

10 5. A process according to any previous claim in which the liquid diluent is a water/alcohol mixture.

6. A process according to any previous claim in which the process is carried out at a pH in the range of 8.5 to 12.

15 7. A process according to any previous claim in which a salt of the desired product is obtained.

8. A process according to any previous claim in which the compound of formula I is isolated as the free heterocycle.

20 9. A process according to any previous claim in which the process is carried out at a temperature in the range of 0 to 150°C.

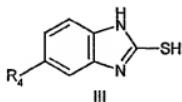
10. A process according to claim 1 in which a compound of formula IIa is reacted with sodium perborate in a mixture of water and methanol at a pH in the range of 8.5 to 10 at a temperature in the range of 15 -115°C to give a compound of formula Ia (omeprazole).

25 11. A process according to any previous claim wherein a purification solvent is added at the end of the oxidation reaction.

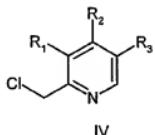
30 12. A process according to claim 11 wherein the purification solvent is a hydrocarbon or an ether.

13. A process according to claim 12 wherein the purification solvent is selected from *tert*-butyl methyl ether or diisopropyl ether.

14. A process according to any previous claim in which the compound of formula 5 II used is prepared by reacting a compound of formula III



or a salt thereof in which R₄ is as previously defined with a compound of formula IV



10 or a salt thereof in which R₁, R₂, and R₃ are as previously defined, optionally in the presence of a base, in a second liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed and is then reacted with a perborate salt without isolation.

15 15. A process according to claim 14 wherein the second liquid diluent is selected from water, a C₁₋₄ alcohol, toluene, tetrahydrofuran, acetone, a C₂₋₆ diol, a C₃₋₆ triol, ethyl acetate or mixtures thereof.

16. A process according to claim 15 wherein the second liquid diluent is the same 20 as the first.

17. A process according to any one of claims 14-16 wherein sodium hydroxide is used as the base.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01574A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 02521 A (KAYANO AKIO ;NIIKAWA NOBUO (JP); EISAI CO LTD (JP); KURODA HIROFUM) 21 January 1999 see the whole document ---	1-17
X	FIESER,M.: "SODIUM PERBORATE" REAGENTS FOR ORGANIC SYNTHESIS, vol. 12, 1986, page 452 XP002109649 NEW YORK see the whole document ---	1-17
X	PAQUETTE,L.A.: "SODIUM PERBORATE" ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS, vol. 7, 1995, pages 4611-4613, XP002109650 CHICHESTER see the whole document ---	1-17

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubt on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date of priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"V" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

19 July 1999

Date of mailing of the international search report

06/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patenttaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01574

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 25 48 340 A (HAESSLE AB) 5 May 1977 see the whole document	1-17
Y	WO 91 19712 A (ASTRA AB) 26 December 1991 see the whole document	1-17
Y	EP 0 197 013 A (HAESSLE AB) 8 October 1986 see the whole document	1-17
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 197 (C-0833), 21 May 1991 & JP 03 052887 A (YOSHITOMI PHARMACEUT IND LTD), 7 March 1991 see abstract	1-17
Y	EP 0 484 265 A (GENESIS PARA LA INVESTIGACION ;ESTEVE QUIMICA SA (ES)) 6 May 1992 see the whole document	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01574

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9902521	A 21-01-1999	JP 11071371	A	16-03-1999
DE 2548340	A 05-05-1977	CA 1055033	A	22-05-1979
		CH 623814	A	30-06-1981
		CS 196290	B	31-03-1980
		CS 196289	B	31-03-1980
		DD 122534	A	12-10-1976
		DK 365978	A	18-08-1978
		DK 372175	A,B,	19-02-1977
		FI 752327	A,B,	16-02-1977
		FR 2392021	A	22-12-1978
		FR 2331340	A	10-06-1977
		GB 1525958	A	27-09-1978
		JP 1364888	C	09-02-1987
		JP 52062275	A	23-05-1977
		JP 61028673	B	01-07-1986
		NL 7513141	A	12-05-1977
		SE 416649	B	26-01-1981
		SU 602118	A	05-04-1978
		US 4045563	A	30-08-1977
		ZA 7506600	A	29-09-1976
		AT 351524	B	25-07-1979
		AT 337697	B	11-07-1979
		CH 623582	A	15-06-1980
		CY 1125	A	19-02-1977
		FI 811747	A,B,	04-06-1978
		HK 8782	A	05-03-1981
		SE 7406513	A	17-11-1976
		MY 15982	A	31-12-1982
		AT 752276	A	15-01-1979
		AT 838075	A	15-11-1976
		IE 42451	B	13-08-1980
WO 9119712	A 26-12-1991	AP 215	A	02-09-1992
		AP 253	A	03-05-1993
		AU 649453	B	26-05-1994
		AU 8009791	A	07-01-1992
		AU 649456	B	26-05-1994
		AU 8061791	A	07-01-1992
		CA 2083606	A	21-12-1991
		CA 2083714	A	21-12-1991
		CN 1058212	A	29-01-1992
		CN 1058213	A	29-01-1992
		CS 9101893	A	17-06-1992
		CS 9101894	A	15-04-1992
		EG 19752	A	31-01-1996
		EP 0593463	A	27-04-1994
		EP 0535081	A	07-04-1993
		FI 925766	A	18-12-1992
		FI 925767	A	18-12-1992
		IL 98472	A	31-08-1995
		LT 1712	A,B	25-08-1995
		LT 1713	A,B	25-08-1995
		LV 10269	A,B	20-10-1994
		LV 10953	A	20-12-1995
		NZ 238546	A	25-03-1994
		OA 9682	A	15-05-1993
		OA 9683	A	15-05-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01574

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9119712	A	PL	166209 B	28-04-1995
		PL	165898 B	28-02-1995
		PT	98035 A	31-03-1992
		PT	98036 A	31-03-1992
		RO	110497 A	30-01-1996
		RO	110493 A	30-01-1996
		WO	9119711 A	26-12-1991
		US	5430042 A	04-07-1995
EP 0197013	A	08-10-1986	JP 61205211 A	11-09-1986
EP 0484265	A	06-05-1992	NONE	